Charge to EPA Science Advisory Board Arsenic Review Panel

Background

There are both natural and anthropogenic sources of arsenic and arsenic containing compounds (or arsenicals). Exposure to arsenicals can be through different environmental media including drinking water, food, soil, and air. EPA assesses and regulates the potential exposure and health risks associated with exposure to arsenic and arsenic containing compounds through several statutory authorities. The Safe Drinking Water Act (SDWA), directs EPA to establish national standards for contaminants including arsenical compounds in public drinking water supplies. EPA's Superfund and Resource Conservation and Recovery Act (RCRA) programs evaluate exposure to arsenic compounds at sites selected for clean up or remediation. Under the Clean Air Act, EPA's Office of Air and Radiation sets emissions standards for sources of arsenic to air. These include standards based on control technology and those based on risks to human health from inhalation of airborne arsenic or ingestion of arsenic arising from air sources. EPA's Office of Pesticide Programs (OPP) evaluates the exposure and health risks associated with arsenicals used as pesticides in the U.S. Under the mandate of the Food Quality Protection Agency (FQPA), EPA must revaluate all pesticide food tolerances (the legal limits of pesticides on/in food or animal feed) in the U.S. by August, 2006. There are several organic arsenic herbicides that are undergoing reregistration and/or tolerance reassessment including cacodylic acid (referred to as dimethylarsinic acid or DMA^V), monosodium, disodium, and calcium salts of methanearsonate acid (MSMA, DSMA, and CAMA, collectively as referred as MMA^V). In 2003, most residential uses of chromated copper arsenate (CCA) as a wood preservative were cancelled.

The health effects of arsenicals have been the subject of two reviews by the National Research Council (NRC) of the National Academy of Sciences (NAS) (NRC 1999; 2001). Since the 2001 NAS review, there has been substantial new information developed on the mode of carcinogenic action and metabolism and toxicokinetics for arsenic and its methylated species, and new epidemiology on inorganic arsenic. The Agency has considered this new science in regards to the hazard characterization required for tolerance assessment of DMA^V (and MMA^V) as described in the draft OPP Science Issue Paper: Mode of Action for Cacodylic Acid (Dimethylarsinic Acid) and Recommendations for Dose Response Extrapolation, and also in the ORD Issue Paper - Cancer Risk Assessment for Organic Arsenical Herbicides: Comments on Mode of Action, Human Relevance and Implications for Quantitative Dose-Response Assessment (See Appendix E). In addition, the Agency has developed a revised hazard and dose response assessment/characterization of inorganic Arsenic (Toxicological review of inorganic arsenic in Support of Summary Information on the Integrated Risk Information System (IRIS)) which relies on the two NRC reviews and

provides an updated human health effects and dose-response assessment for inorganic arsenic. The Agency seeks comment and advice from the SAB on the scientific soundness of major science conclusions drawn in these two documents regarding the carcinogenic assessments of DMA^V and inorganic arsenic and the appropriateness of the Agency's application of its own Guidelines for Carcinogen Risk Assessment for arsenicals.

Overview of Science and Assessment Issues

Ingestion of inorganic arsenic has been demonstrated to cause cancer of the skin, lung, and urinary bladder in humans. Historically, standard chronic bioassays with exposure to inorganic arsenic in rodents have been negative for increased tumor formation. There are, however, more recent studies at high doses, in transgenic animals, and following transplacental exposures which have demonstrated cancer potential in rodent studies following exposure to inorganic arsenic. The NRC 1999 report advises that the bladder and lung cancer human mortality data, particularly from the southwestern Taiwanese studies provide the best dose-response data for evaluating the long-term effects of ingestion of inorganic arsenic. In the 2001 NRC report, a number of recommendations were made to EPA to revise the oral cancer slope for inorganic arsenic. Given the available database, and recognizing that the mode(s) of action by which inorganic arsenic causes cancer has not been fully established, the draft Toxicological Review of Arsenic, consistent with advice from the NRC uses linear low dose extrapolation to estimate cancer risks from ingestion to arsenic at low dose and has addressed many of the NRC recommendations.

In approaching the cancer assessment on the pesticide cacodylic acid (DMA^V), an organic arsenical, EPA has confronted a number of challenging issues. No human epidemiological information is available for DMA^V. Rodent cancer bioassay data have shown that dietary administration of DMA^V can result in bladder carcinogenesis in the rat. DMA, however, is a key urinary metabolite from exposure to inorganic arsenic. Thus, the question is raised regarding the extent the cancer epidemiology on inorganic arsenic may provide an appropriate dataset or may inform the low dose extrapolation for the cancer risk associated with direct exposure to DMA^V. Available *in vivo* and *in vitro* pharmacokinetic, metabolism studies, and toxicology studies were reviewed to address this issue. The draft OPP Science Issue Paper states that the evidence indicates inorganic arsenic and DMA^V have different pharmacokinetic and pharmacodynamic characteristics, EPA proposes to use the rat bioassay data on DMA^V to estimate its cancer risk. The ORD Issue Paper (Appendix X of the OPP Science Issue Paper: Cancer Mode of Action of Cacodylic Acid (Dimethylarsinic Acid) and Recommendations for Dose Response Extrapolation) provides additional discussion on the MOA issues and perspective on the nexus between science issues for organic and inorganic arsenicals. **T**he use of mode of action data in the assessment of potential carcinogens is a main focus of EPA's 2005 cancer

guidelines. Mode of action data are available on DMA and were evaluated to guide the low dose extrapolation. The Agency seeks comments and advice from the SAB on key science issues concerning (A) the metabolism and toxic responses of arsenic species, (B) the mode of action for carcinogenesis and implications for dose-response extrapolation for DMA^V and inorganic arsenic, (C) the selection of data for dose-response, and (D) approaches to low-dose extrapolation. In addition, the Agency is requesting comment on the implications of newer epidemiology and the incorporation of the 2001 NRC recommendation on modeling the human cancer data for inorganic arsenic.

Issues and Charge Questions

A. Metabolism and Toxic Responses of Arsenic Species

A1. Metabolism and pharmacokinetics

Evidence from *in vivo* and *in vitro* metabolism and pharmacokinetic studies with humans and laboratory animals suggests that the efficiency of the methylation reaction(s) and cellular uptake varies based on which arsenical compound is administered exogenously. Most available studies suggest that the metabolic process in most mammals is primarily a one-way process and that following direct exposure to DMA^V significant amounts of iAs^{III}, iAs^V, MMA^{III}, or MMA^V at the target tissue are not expected.

Please comment on how pharmacokinetic processes are best considered regarding the use of data derived from direct DMA^V exposure versus direct iAs exposure for cancer risk assessment.

A2. Response to mixtures of metabolites

Tumorigenic profiles vary based on which arsenical compound is administered exogenously. *In vivo* and *in vitro* studies indicate that each of the arsenical compounds exhibit similarities and differences in their profiles of biological activities. Direct exposure to iAs^{III} or iAs^V is expected to result in more of a mixture of toxic metabolites than for direct exposure to DMAv; the mixture of metabolites is expected to vary based on which chemical is administered exogenously. The potential mixture of metabolites following direct exposure to DMA^V appears less complex as compared to iAs.

Given the toxicological response profiles observed following direct exposures to iAs versus MMA^v and DMA^V, and the differences in human and rodent toxicologic responses to arsenicals, please comment on the use of data derived from rodent exposures to the organic arsenicals

versus use of data derived from direct iAs human exposure, in the DMA^V assessment.

B. Modes of Carcinogenic Action for DMA^V and Inorganic Arsenic

B1. Mode of action of DMA^v

When relying on laboratory animal data, two critical assumptions are made: (i) data on animal tumors are predictive of human cancer, and (ii) animal tumor effects found at high experimental doses predict human risk at lower exposures. An understanding of a chemical mode of carcinogenic action can help inform the above assumptions. In the case of DMA^V, mode of action (MOA) data are available and were evaluated using the framework described in EPA's cancer guidelines.

Please comment on the sufficiency of evidence to establish the animal mode of carcinogenic action for DMA^V. Are the scientific conclusions sound and consistent with the available evidence on DMA^V and the current state of knowledge for chemical carcinogenesis.

Please comment on whether the key events in DMA's mode of action are supported by the available data. Specifically comment on the role of: a) reactive oxygen species in producing chromosomal damage and the strength of the evidence supporting oxidative damage as a causal key event in DMA^V/DMA^{III}'s mode of carcinogenic action versus an associative event or a secondary consequence of cytotoxicity; b) cell proliferation and cytotoxicity and the strength of the evidence as causal key events in DMA^V/DMA^{III}'s mode of carcinogenic action versus associative or secondary events, and c) other potential modes of action that have substantial scientific support that may be contributing to the carcinogenicity of DMA.

B2. Human relevance of animal DMA^V MOA

There are little or no scientific data to suggest that if sufficient DMA^{III} were present, key precursor events and ultimately tumor formation would not occur in humans directly exposed to DMA^V .

Please comment on the relevance of the postulated key events (see B1) to tumors in humans.

Please comment on how, if at all, differences in the human population vs. experimental animals should be accounted for in the risk assessment for DMA^V.

There are little to no chemical specific data regarding an increased susceptibility of humans for bladder tumor development during different life stages.

Please comment on the Agency's conclusion that the young are likely to respond like the adult to the formation of bladder tumors following exposure to DMA.

B3. Modes of carcinogenic action from exposure to inorganic arsenic

Inorganic arsenic (iAs) undergoes successive methylation steps in humans, resulting in the intermediate production of iAs^{III}, MMA^{V}, MMA^{III}, DMA^{V}, and DMA^{III}. Each arsenical metabolite exhibits its own toxicity.

Please comment on the conclusion that the available data support the hypothesis that multiple modes of action may be operational following exposure to inorganic arsenic.

C. Selection of Data for Dose-Response Assessment

C1. Use of animal data for DMA^{V}

A number of different rodent bioassays (standard bioassay, transgenic animals, susceptible rodent strains, initiation and promotion studies) are available on DMA^{V}.

Please comment on the use of the bladder tumor data from the DMA^{V} rat bioassay as the most suitable dataset for quantifying potential human cancer risk to DMA^{V}, including the weight of evidence to support this conclusion.

Please comment on whether the iAs epidemiology data can be used to inform the DMA^{V} dose-response assessment derived from rat data with DMA^{V}. If so, please discuss how such information might be used. (See Appendix).

C2. Use of human epidemiological data from direct iAs exposure

Since the NRC (2001) report on iAs, an additional body of literature has developed describing epidemiology data from populations in the US exposed to iAs in drinking water.

Does the SAB agree that the Taiwanese dataset remains the most appropriate choice for estimating cancer risk in humans? Please discuss the rationale for your response.

Do these data provide adequate characterization of the impact of childhood exposure to iAs? Please discuss the rationale for your response.

D. Approaches to Low-Dose Extrapolation for Inorganic Arsenic and DMA^V

D1. Mode of carcinogenic action understanding for $DMA^{V/III}$ and implications for dose response extrapolation to estimate human cancer risk.

The use of mode of action data in the assessment of potential carcinogens is a main focus of EPA's 2005 cancer guidelines. As stated in these guidelines "The approach to dose-response assessment for a particular agent is based on the conclusion reached as to its potential mode(s) of action". Although a biological-based model is the preferred approach to estimating cancer risk, there are insufficient data on DMA^V to support development of such a model.

Please comment on the scientific evidence and biological rationale in support of nonlinear versus linear low dose extrapolation approaches, which approach is more consistent with the available data on DMA^V and current concepts of chemical carcinogenesis, and how scientific uncertainty should most appropriately be incorporated into low-dose extrapolation.

D2. Implementation of the recommendations of the NRC (2001)

EPA has determined that the most prudent approach for modeling cancer risk from exposure to iAs is to use a linear model because there are significant remaining uncertainties regarding which of the metabolite(s) may be the ultimate carcinogenic moiety and whether or not mixtures of toxic metabolites interact at the site(s) of action.

Does the panel concur with the selection of a linear model following the recommendations of the NRC (2001) to estimate cancer risk at this time? Please discuss your response in light of the highly complex mode of action for iAs with its metabolites.

D3. EPA re-implemented the model presented in the NRC (2001) in the language R as well as in an Excel spreadsheet format. In addition, extensive testing of the resulting code was conducted.

Please comment upon precision and accuracy of the re-implementation of the model.

D4. Available literature describing drinking water consumption rates for the southwestern Taiwanese study population

NRC (2001) stated that the drinking water consumption rate, as well as variability of that rate in both US and Taiwanese populations, are important factors to consider. In calculating risk estimates for U.S. populations exposed to arsenic through drinking water, NRC used a drinking water consumption rate of 1 L/day for the US population and two possible consumption rates for the Taiwanese population: 1 L/day (identical to the US population) and 2.2 L/day with little or no supporting rationale. Since publication of NRC 2001, a number of new studies have become available and are summarized in the Cancer Slope Factor Workgroup Issue Paper. Agency reviews of the relevant literature suggests that the mean drinking water for the Taiwanese study population consumption rate is between 1 to 4.6 L/day. EPA's current cancer modeling includes water intake adjustments for 2.0 and 3.5 L/day.

What drinking water value does the panel recommend for use in deriving the cancer slope factor for inorganic arsenic?

D5. Selection of an estimate of dietary intake of arsenic from food

The issue of intake of arsenic from food (e.g., dry rice, sweet potatoes) has been distinguished from the issue of intake of arsenic from drinking water. The NRC addressed the issue of arsenic in food by determining how sensitive the calculation of ED_{01} was to the consumption rate. NRC found that changing the consumption rate from 50 µg/day to 30 µg/day did not change the calculated ED_{01} significantly (about 1% difference). Since the publication of NRC 2001, a number of new studies have become available, summarized in the Cancer Slope Factor Workgroup Issue Paper. EPA's current cancer modeling includes dietary intake adjustments for 0, 10, 30, and 50 µg/day.

What background dietary intake of arsenic value does the panel recommend for both the control population and study population of Southwestern Taiwan used in deriving the cancer slope factor for inorganic arsenic?

List of SAB Review Materials

1. OPP Science Issue Paper: Cancer Mode of Action of Cacodylic Acid (Dimethylarsinic Acid) and Recommendations for Dose Response Extrapolation and also in the ORD Issue Paper on the Implications of DMA (Dimethylarsinic Acid) Mode of Action Data *including Appendix X: ORD Issue Paper on the Cancer Mode of Action of Cacodylic Acid (Dimethylarsinic Acid) and Recommendations for Dose Response Extrapolation*

2. OW: Toxicological Review of Inorganic Arsenic in Support of Summary Information on the Integrated Risk Information System (IRIS)

3 Cancer Slope Factor Workgroup Issue Paper

Critical Cited References

1. U.S. EPA. (2005) Guidelines for carcinogen risk assessment. Risk Assessment Forum, Washington, DC; EPA/630/P-03/001B. Available from: http://www.epa.gov/iris/backgr-d.htm

2. NRC (2001) Arsenic in drinking water. 2001 update. National Academy Press, Washington, D.C. http://www.nap.edu/openbook/0309076293/html/R1.html.

3. NRC (1999) Arsenic in drinking water. National Academy Press, Washington, D.C. http://www.nap.edu/openbook/0309063337/html/R1.html.